Comments on the "SYN1 - DRAFT Waiver based on RISK21 Approaches for Chronic/Carcinogenicity Studies"

The comments in this document represent the opinions of a subset of members from the Office of Pesticide Programs Cancer Assessment Review Committee (CARC) and the Hazard and Science Policy Committee (HASPOC). The opinions expressed are those of the individual scientists and do not represent opinions of the full committees and are not considered committee decisions.

The general impression was that chronic/carcinogenicity waiver requests would be most appropriate in cases where there is a very strong exposure argument or where there is a lot of information available on the class/group of chemicals and this surrogate class/group of chemicals should be the primary focus which each section of the document is tied back too. Comments on specific sections of the document are presented below:

1.0 INTRODUCTION:

- More information on the exposure potential for the active ingredient should be presented in the introduction. For example, is long term exposure expected? Via which route(s)? Setting the stage for exposure up front is important and part of the WOE.

- The exposure component can be important for some pesticides with limited exposure potential – e.g., if you need a q* of 1.5 to have a risk of concern because of low app rates, etc., this could weigh heavily into not needing a chronic/cancer study. Generally, risk-based arguments, rather than just hazard-based arguments, will drive waiver determinations since the final decision is always our ability to make a reasonable certainty of no harm call.

2.0 CRITERIA FOR WAIVERS WITH FOOD USE PESTICIDES

2.1 Knowledge of intended use indication and class of chemistry

- Is there more information that could be pulled from this class of chemistry that would be helpful in understanding how they work?

- More information such as physical and chemical properties, etc., is needed.

2.2 Metabolic Profile

- This section should be presented in context for the need for a long-term study. Would accumulation of compound be expected and its impact on tumor development? How does the ADME for this compound compare to others in the class? And what did the long-term studies for similar ADME chemicals show?

- Overall there needs to be a better connection on how the ADME information informs the need for a rodent chronic/cancer study. For example, in the ADME section on page 4, the statement: "Radioactivity was widely distributed, with the highest concentrations of radioactivity observed in the liver and kidney at all

sample time points between 0.5h and 120h" – provide information on why there is or is not concern in these tissues after a chronic exposure. In the discussion of the metabolism of SYN1 in rats, how does that information help inform the need for a chronic/cancer study?

- One suggestion was to change the format of this section, with bullet points covering each part of ADME and indicating why it is relevant. For example; it was shown that absorption decreases as dose increases which suggests that X, Y Z. For excretion, what is the half life? Is this chemical quickly excreted which may mean there is less potential for accumulation over time?

- For ADME data, the absorption, distribution, and excretion data cannot inform our need for a chronic study without a better understanding of the toxicity of the parent and metabolites. One case where metabolism information may help EPA determine whether long-term data are needed, are for chemicals that are part of a class where a number of other chemicals already have chronic data. In those cases, if currently registered chemicals have similar metabolic products to a proposed chemical, that information could inform the potential chronic toxicity for the shared metabolites. Do they have similar metabolic pathways? Do they have similar tissue distribution and plasma kinetics?

- This mock example is an SDHI inhibitor. Many of them have a 3-(difluoromethyl)-1H-pyrazole-4-carboxylic acid group which is a major metabolite for which have significant amount of toxicity data.

2.2.2 Toxicokinetics

- The toxicokinetic information provided is helpful. The only comment was to provide an overall summary statement at the end of this section, i.e., what is the bottom line in the context of this waiver request? It also may be helpful to have conclusions statements for each section, relating it back to how the data presented in that section support the waiver request.

- From a toxicokinetic standpoint should we expect this chemical to behave like the rest of the class and why?

2.3 Results of all studies, including in vitro and repeated dose studies and mechanistic information.

- One suggestion was condensing sections 2.3 and 2.4 into one section called "evidence to inform carcinogenic potential in guideline studies". Describe the target organs and doses in which effects where seen, that there was no evidence of genotoxicity and any other information that may be relevant to carcinogenicity (BrdU staining results, for example) instead of simply listing all effects observed.

2.3.2 Short-term Toxicity

- Suggestion to include any relevant information from the rat developmental and rat reproduction studies that would inform whether progression of toxicity is observed and if target organs are consistently observed across rat studies. Were liver and thyroid targets in those studies as well? Was other toxicity seen in those studies (i.e., other target organs)?

- Address why the NOAEL from the 90-day study is lower than the 28-day study. This may go against not expecting increased toxicity or cancer with longer term studies. Are these data consistent with what would be expected based on the ADME data? Need to tie it together.

- Recommend reporting only NOAEL/LOAEL, not NOEL/LOEL, and reporting doses as mg/kg/day, where appropriate.

- Present values for % changes for parameters rather than using terms such as "higher liver weight" or arrows indicating the direction of the effect. We need to know the magnitude of the changes to help inform our decisions. This applies to the entire document, including toxicity summary tables.

- Discuss how do the 28-day studies in rat and mouse compare to 90-day studies for that species? Is there progression of toxicity?

- 28-day Mouse: include the results for cell proliferation

- Discuss any sex differences in the responses when observed.

2.4 Genetic Toxicity Study Results

- In this case, the mouse micronucleus test did not assess bone marrow so more information on the clinical signs observed is needed; type of effect and magnitude of clinical signs; especially given the positive in vitro clastogenic responses reported. Clearly need to absolutely rule out in vivo genotoxicity to support this type of waiver.

2.5 Special Studies and Endpoints

- In the first paragraph of this section, what information was used to draw these conclusions in mouse vs rat? Why were liver tumor a lower likelihood? How did you come to conclusion to focus on the mouse? What other information from the class was used to make this assumption?

- Is there any ADME or structural information to support why this chemical may be more like SDHI inhibitors that result in liver and thyroid tumors versus SDHI inhibitors that do not? How might that information be used to support using

earlier key events as regulatory endpoints and not requiring long-term studies?

- Typically, the types of data presented in this section would be used to support a proposed MOA for tumors. In the context of this case there are no carcinogenicity studies. Suggest including a table showing dose and temporal concordance for earlier key events, obviously you will not have tumors, but there are other key and associative events that should line up according to dose and temporal observations from early (2-day) to 90-day exposures.

- The Agency considers the CAR-mediated MOA to be relevant to humans and would not come to the same conclusion as the waiver states in Section 2.5.3.

- More detail is needed for the potential thyroid MOA investigations (Section 2.5.4) to support the conclusions. Section needs to be expanded and results presented.

2.6 Evidence of Hormonal Perturbation

- More information is needed in this section. What is the evidence to support that the statement that a lack of estrogenic or other hormonal perturbation? Were hormones measured in any of the studies?

2.8 Read-across – to other molecules in the same class

- It is not clear what parts of this section are supporting non-cancer/chronic dietary study waiver and what parts are supporting the carcinogenicity studies waiver. Suggest making distinct sections to address them separately. Need to differentiate non-cancer chronic from cancer assessment.

- Why did the retrospective analysis look at only 9 instead of the all 13 SDHIs?

- Need a better explanation of how the 2.1 factor was calculated. A matrix to outline all the data to support the read across would be very helpful.

- A spreadsheet or data matrix of the results for the studies for this chemical and how they compare to the surrogates, especially when it comes to the pre-neoplastic lesions and other biomarkers for the toxicity and cancer observed for the SAR chemicals would be helpful.

- For the 9.0 mg/kg/day estimate for chronic/carcinogenicity study for SYN1: How does this compare to the NOAELs from chronic studies with similar molecules? How similar are the other molecules in the class to SYN1? A discussion of endpoints and structure for the other chemicals in the class would be important.

- It is not clear why one would assume the same 2.1 factor derived from the rat data would apply to mice for a chronic NOAEL. Why wouldn't the same

analysis be done for that database?

- The document states that "the extrapolated estimates of chronic NOAELs are very similar for SYN1 in mice and in rats. In both species, the NOAELs were lower in males than in females." However, the LOAEL in the 90-day mouse is higher than the 90-day rat; therefore, it is not clear why one would expect the extrapolated estimates to be similar for mice and rats.

- For the tumor comparisons (page 20), suggest a matrix be developed for each tumor type that was observed across all the chemicals in the class. This would be easier to display than a couple of bullets for each section.

- Are there any chemicals in this class that form liver or thyroid tumors via modes of action other than CAR-activation and UDPGT-induction?

- Do you have data on other potential MIEs or key events to adequately exclude alternative tumor MOAs?

- In the discussion of "Other less common tumors", this section needs to be expanded. Needs more information around whether these other tumors would be expected for SYN1. Were there indicators for these tumors in the shorter-term studies for these chemicals? There needs to be more information on how some other tumor would not be expected for SYN1. For example, would the brain astrocytomas, ovarian tubulostromal tumors and histiocytic sarcomas seen for penflufen have been predicted based on the tox database for penflufen? And how is this one different from SYN1? Need to state whether these would be potential tumors for SYN1 and why or why not.

2.9 Margins of exposure based on existing data and proposed exposure scenarios.

- In Table 5, do that values also include drinking water? Or food only? Where is the information on drinking water and the assumptions used to generate the estimates? Water alone is what % of cPAD? This information should be included in this section.